IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Gosselin *et al.*

Filed: Herewith

Serial No.: Unassigned
Continuation of U.S.S.N. 09/371,747 Filed: August 10, 1999

Group Art Unit: 1623
Examiner: L. Eric Crane

For: β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

December 14, 2001

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified application as follows.

In the Specification

Please amend the paragraph on page 1, beginning on line 3, with the following rewritten paragraph:

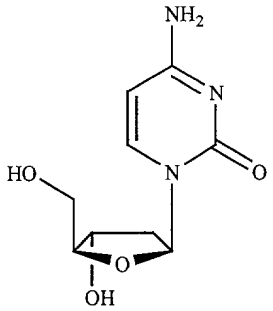
-- This application is a continuation application of U.S. patent application number 09/371,747 filed on August 8, 1999, now allowed, which claims priority to U.S. provisional application number 60/096,110, filed on August 10, 1998 and U.S. provisional application number 60/131,352, filed on April 28, 1999. --

In the Claims

Please cancel claims 1-12.

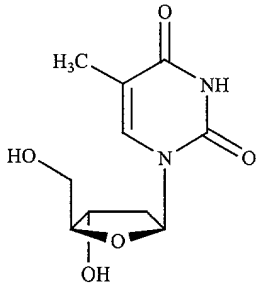
Please add the following claims:

13. A method for the treatment or prophylaxis of a hepatitis B virus infection in a human comprising administering an effective amount of β-L-2'-deoxycytidine of the formula:



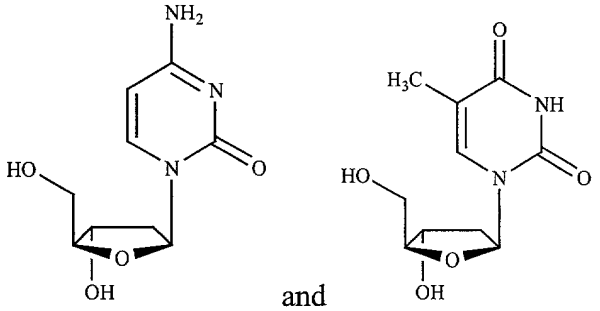
or pharmaceutically acceptable salt thereof.

14. A method for the treatment or prophylaxis of a hepatitis B virus infection in a human comprising administering an effective amount of β-L-thymidine of the formula:



or pharmaceutically acceptable salt thereof.

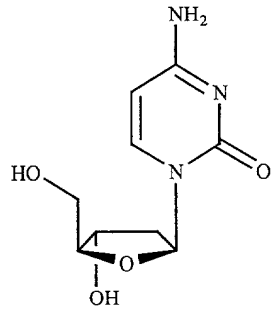
15. A method for the treatment or prophylaxis of a hepatitis B virus infection in a human comprising administering an effective amount of a combination of the following nucleosides:



and

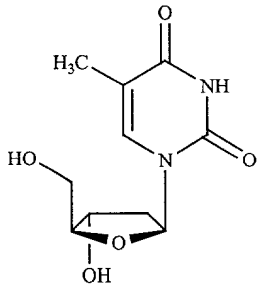
or a pharmaceutically acceptable salt thereof.

16. A method for the treatment or prophylaxis of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine (L-FMAU), β-D-2,6-diaminopurine dioxolane (DAPD), famciclovir, penciclovir, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.

17. A method for the treatment or prophylaxis of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine (L-FMAU), β-D-2,6-diaminopurine dioxolane (DAPD), famciclovir, penciclovir,

2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.

18. The method of claim 13, wherein the β-L-2'-deoxycytidine is at least 95% in its designated enantiomeric form.

19. The method of claim 13, wherein the β-L-2'-deoxycytidine is administered in a pharmaceutically acceptable carrier.

20. The method of claim 19, wherein the pharmaceutically acceptable carrier is suitable for oral delivery.

21. The method of claim 19, wherein the pharmaceutically acceptable carrier is suitable for intravenous delivery.

22. The method of claim 19, wherein the pharmaceutically acceptable carrier is suitable for parenteral delivery.

23. The method of claim 19, wherein the pharmaceutically acceptable carrier is suitable for intradermal delivery.

24. The method of claim 19, wherein the pharmaceutically acceptable carrier is suitable for subcutaneous delivery.

25. The method of claim 19, wherein the pharmaceutically acceptable carrier is suitable for topical delivery.

26. The method of claim 19, wherein the compound is in the form of a dosage unit.

27. The method of claim 26, wherein the dosage unit contains 10 to 1500 mg of the compound.

28. The method of claim 26 or 27, wherein the dosage unit is a tablet or capsule.

29. The method of claim 14, wherein the β-L-thymidine is at least 95% in its designated enantiomeric form.

30. The method of claim 14, wherein the β-L-thymidine is administered in a pharmaceutically acceptable carrier.

31. The method of claim 29, wherein the pharmaceutically acceptable carrier is suitable for oral delivery.

32. The method of claim 29, wherein the pharmaceutically acceptable carrier is suitable for intravenous delivery.

33. The method of claim 29, wherein the pharmaceutically acceptable carrier is suitable for parenteral delivery.

34. The method of claim 29, wherein the pharmaceutically acceptable carrier is suitable for intradermal delivery.

35. The method of claim 29, wherein the pharmaceutically acceptable carrier is suitable for subcutaneous delivery.

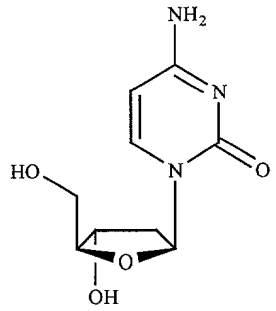
36. The method of claim 29, wherein the pharmaceutically acceptable carrier is suitable for topical delivery.

37. The method of claim 29, wherein the compound is in the form of a dosage unit.

38. The method of claim 37, wherein the dosage unit contains 10 to 1500 mg of the compound.

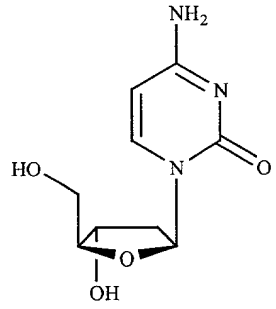
39. The method of claim 28 or 38, wherein the dosage unit is a tablet or capsule.

40. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



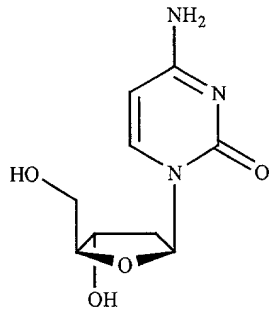
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), or its pharmaceutically acceptable salt thereof.

41. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



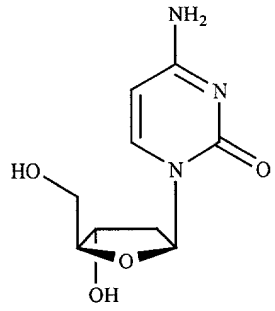
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), or its pharmaceutically acceptable salt thereof.

42. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



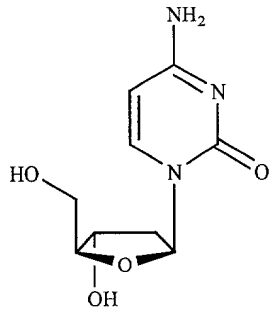
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine (L-FMAU), or its pharmaceutically acceptable salt thereof.

43. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



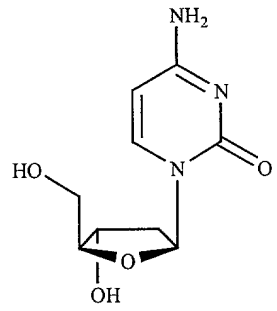
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-D-2,6-diaminopurine dioxolane (DAPD), or its pharmaceutically acceptable salt thereof.

44. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



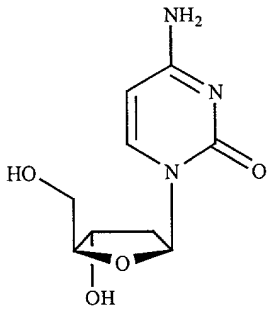
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of famciclovir, or its pharmaceutically acceptable salt thereof.

45. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



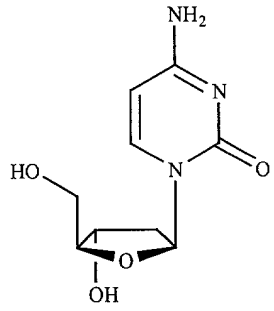
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of penciclovir, or its pharmaceutically acceptable salt thereof.

46. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



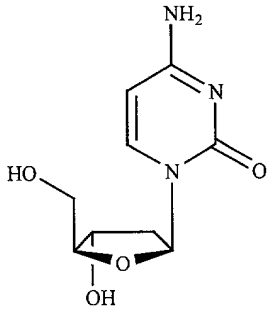
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), or its pharmaceutically acceptable salt thereof.

47. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



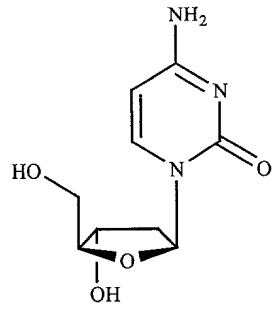
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil), or its pharmaceutically acceptable salt thereof.

48. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



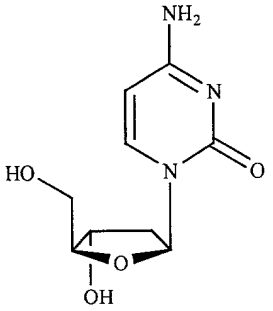
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of lobucavir, or its pharmaceutically acceptable salt thereof.

49. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



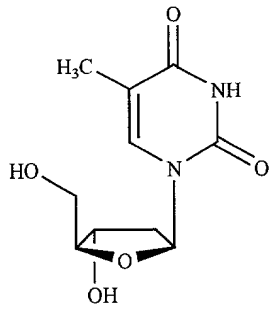
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ganciclovir, or its pharmaceutically acceptable salt thereof.

50. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



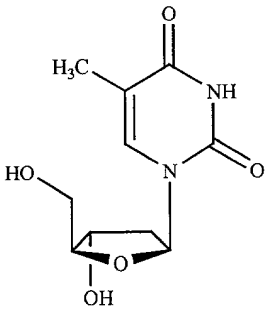
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ribavirin, or its pharmaceutically acceptable salt thereof.

51. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



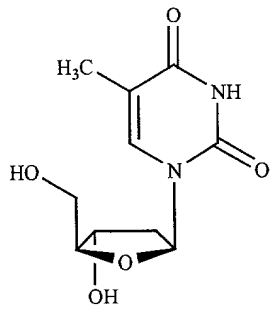
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), or its pharmaceutically acceptable salt thereof.

52. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



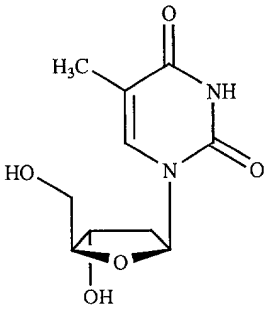
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), or its pharmaceutically acceptable salt thereof.

53. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



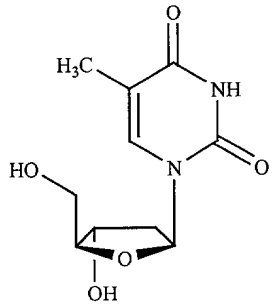
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine (L-FMAU), or its pharmaceutically acceptable salt thereof.

54. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



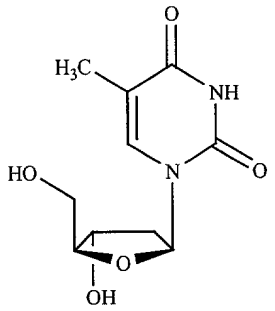
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-D-2,6-diaminopurine dioxolane (DAPD), or its pharmaceutically acceptable salt thereof.

55. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



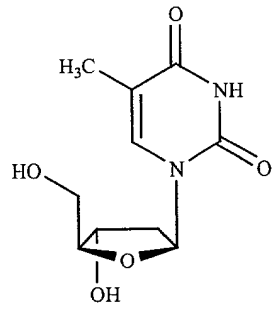
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of famciclovir, or its pharmaceutically acceptable salt thereof.

56. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



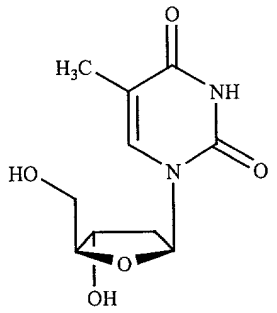
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of penciclovir, or its pharmaceutically acceptable salt thereof.

57. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



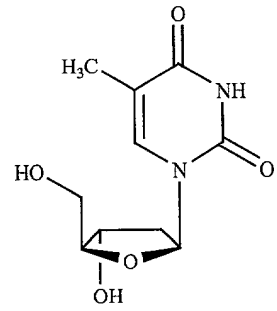
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), or its pharmaceutically acceptable salt thereof.

58. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



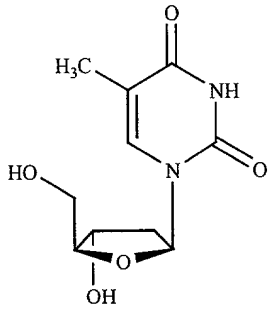
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil), or its pharmaceutically acceptable salt thereof.

59. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



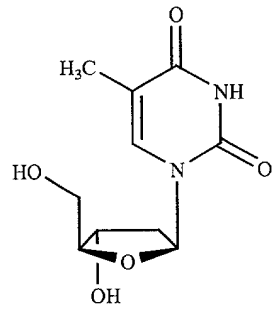
or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of lobucavir, or its pharmaceutically acceptable salt thereof.

60. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ganciclovir, or its pharmaceutically acceptable salt thereof.

61. A method for the treatment or prophylaxis of a hepatitis B virus infection in a host comprising administering an effective amount of a compound of the formula:



or its pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ribavirin, or its pharmaceutically acceptable salt thereof.

62. The method of any one of claims 40 - 61 wherein the host is a human.

Remarks

New claims 13-39 and 62 are directed to methods for the treatment of a hepatitis B virus infection in a human comprising administering β-L-2'-deoxycytidine or β-L-thymidine, optionally in combination or alternation with another effective agent for the treatment of hepatitis B virus infection, which finds support on page 4, lines 6-10 of the specification. New claims 40-61 are directed to methods comprising administering β-L-2'-deoxycytidine or β-L-

thymidine in combination or alternation with a specific effective agent for the treatment of hepatitis B virus infection, namely β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), *cis*-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxa-thiolane (FTC), β-L-2'-fluoro-5-methyl-arabinofuranolyl-uridine (L-FMAU), β-D-2,6-diamino-purine dioxolane (DAPD), famciclovir, penciclovir, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir or ribavirin. Support for these claims can be found on page 17, lines 15-19 of the specification.

This Preliminary Amendment is filed without fee. Although Applicants believe the amount of the fee is correct, the Commissioner is authorized to charge any deficiency to Deposit Account 11-0980.

Respectfully submitted,

Sherry M. Knowles
Reg. No. 33,052

Date: December 14, 2001

Enclosure: Marked up version of amendment

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Version with Markings to Show Changes Made

In the Specification

The paragraph on page 1, beginning on line 3, has been amended as follows:

This application is a continuation application of U.S. patent application number 09/371,747 filed on August 8, 1999, now allowed, which [~~This application~~] claims priority to U.S. provisional application **number** [~~U.S.S.N.~~] 60/096,110, filed on August 10, 1998 and **U.S. provisional application number** [~~U.S.S.N.~~] 60/131,352, filed on April 28, 1999.